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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: SEQUENCES SPECIFICALLY DELETED MYCOBACTERIUM TUBERCULOSIS GENOME AND THEIR USE
IN DIAGNOSTICS AND AS VACCINES

(57) Abstract: The present invention is the identification of a nucleotide sequence which make it possible in particular to distinguish
an infection resulting from the vast majority of *Mycobacterium tuberculosis strains* from an infection resulting from *Mycobacterium
africanum*, *Mycobacterium canettii*, *Mycobacterium microti*, *Mycobacterium bovis*, *Mycobacterium bovis BCG*. The subject of the
present invention is also a method for detecting the sequences in question by the products of expression of these sequences and the
kits for carrying out these methods. Finally, the subject of the present invention is novel vaccines.

INTERNATIONAL SEARCH REPORT

Internat. Application No.
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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, MEDLINE, EMBL, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COLE S T ET AL: "Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 393, 11 June 1998 (1998-06-11), pages 537-544, XP002087941 ISSN: 0028-0836 figure 1 table 1	1-5,9, 15-19, 21,29, 30,42, 51-53
X	& DATABASE GENBANK 'Online! NCBI; 7 September 2001 (2001-09-07) COLE S.T. ET AL.: "Mycobacterium tuberculosis H37Rv complete genome." retrieved from HTTP://WWW.NCBI.NLM.NIH.GOV Database accession no. NC_000962 the whole document --- -/--	1-5,9, 15-19, 21,29, 30,42, 51-53

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *Z* document member of the same patent family

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INTERNATIONAL SEARCH REPORT

Internat
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE GENBANK 'Online! NCBI; 3 August 2001 (2001-08-03) COLE S.T. ET AL.: "Mycobacterium tuberculosis H37Rv complete genome; segment 69/162" retrieved from HTTP://WWW.NCBI.NLM.NIH.GOV Database accession no. Z74020 XP002206252 the whole document	1-5, 9, 15-19, 21, 29, 30, 42, 51-53
A	WO 00 55362 A (BILLAULT ALAIN ;COLE STEWART (FR); GARNIER THIERRY (FR); GORDON ST) 21 September 2000 (2000-09-21) page 5, line 9 -page 17, line 21 page 22, line 15 -page 32, line 3 figure 1D tables 1-3 claims 3, 6, 14	46-52, 55, 58, 59
A	US 6 291 190 B1 (BEHR MARCEL ET AL) 18 September 2001 (2001-09-18) column 11, line 66 -column 18, line 58 table 1	46-52, 55, 58, 59
A	MAHAIRAS G G ET AL: "MOLECULAR ANALYSIS OF GENETIC DIFFERENCES BETWEEN MYCOBACTERIUM BOVIS BCG AND VIRULENT M. BOVIS" JOURNAL OF BACTERIOLOGY, WASHINGTON, DC, US, vol. 178, no. 5, 1 March 1996 (1996-03-01), pages 1274-1282, XP000647583 ISSN: 0021-9193 cited in the application figure 2	46-52, 55, 58, 59
A	GORDON S V ET AL: "IDENTIFICATION OF VARIABLE REGIONS IN THE GENOMES OF TUBERCLE BACILI USING BACTERIAL ARTIFICIAL CHROMOSOME ARRAYS" MOLECULAR MICROBIOLOGY, BLACKWELL SCIENTIFIC, OXFORD, GB, vol. 32, no. 3, May 1999 (1999-05), pages 643-655, XP000933429 ISSN: 0950-382X cited in the application tables 1-3	46-52, 55, 58, 59

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INTERNATIONAL SEARCH REPORT

Internal application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE TAXONOMY BROWSER 'Online! NCBI; Host: http://www.ncbi.nih.gov, "Mycobacterium tuberculosis complex" XP002206354 Link: http://www.ncbi.nlm.nih.gov/Taxonomy/Browse/r/wwwtax.cgi?id=77643 Retrieved on: 16.07.2001 the whole document</p> <p>---</p>	45-47, 51,55
A	<p>SREEVATSAN SRINAND ET AL: "Restricted structural gene polymorphism in the Mycobacterium tuberculosis complex indicates evolutionarily recent global dissemination." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 94, no. 18, 1997, pages 9869-9874, XP002206250 1997 ISSN: 0027-8424 page 9870, left-hand column table 1 figure 1</p> <p>---</p>	46-51,55
T	<p>BROSCH R ET AL: "A new evolutionary scenario for the Mycobacterium tuberculosis complex." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 99, no. 6, 19 March 2002 (2002-03-19), pages 3684-3689, XP002206251 http://www.pnas.org March 19, 2002 ISSN: 0027-8424 the whole document</p> <p>---</p>	1-56,58, 59
T	<p>-& DATABASE GENBANK 'Online! NCBI; 16 March 2002 (2002-03-16) BROSCH R ET AL.: "Mycobacterium tuberculosis mmpS6 gene and mmpL6 gene" retrieved from HTTP://WWW.NCBI.NLM.NIH.GOV, accession no. AJ426486 XP002251350 the whole document</p> <p>-----</p>	1-56,58, 59

INTERNATIONAL SEARCH REPORT

Int

Application No.
PCT/83/03/00986

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 6,27-29,51,52,58-59 (partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 6,27-29,51,52,58-59 (partially)

Present claims 6, 27-29, 51, 52, 58 and 59 relate to products defined by reference to a desirable characteristic or property, namely

- a fragment specifically deleted in certain M. tuberculosis strains (claim 6),
- primers defined by reference to claim 25 which relates to a method wherein primers able of amplifying a genomic region harbouring the TbD1 deletion are used (claims 27-29)
- primers specific for various genetic markers (claim 51(b) and claim 52 (b) and (c))
- polynucleotide sequences capable to hybridise with the genetic the RD1, RD4, RD9 and TbD1 genetic markers (claim 58)
- a polypeptide encoded by each of the RD1, RD4, RD9 and TbD1 genetic markers capable to react with an antibody/immune serum raised against the same immunogenic molecules or fragments thereof (claim 59).

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Art. 6 PCT and is reproducible within the meaning of Art. 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Art. 6 PCT). An attempt is made to define the products by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to

- a nucleic acid as defined by SEQ ID Nos. 4 and 13-16 or their complementary sequences, which nucleic acid is deleted in certain M. tuberculosis strains, but present in other Mycobacteria of the Mycobacterium tuberculosis complex (claim 6)
- the sequences defined in claim 26 (claims 27-29)
- the primer pairs specific for RD4 and RD9 as given by Table 1 (claim 52)
- the oligonucleotide probes/primers specific for RD1, RD4 or RD9 as represented in Table 1, or specific for TbD1 as defined by claim 7 (claim 58)
- the polypeptides as defined by claim 16 (claim 59).

As the polypeptides encoded by RD1, RD4 and RD9 referred to in claim 59 are not defined, they were not searched at all.

Additionally, claim 51 relates to an extremely large number of possible products. In fact, claim 51 contains so many options, variables and possible permutations that a lack of clarity and conciseness within the meaning of Art. 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. Said claim relates to any combination of

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

primers defined in claims 1-14, 17 and 18 with at least one primer pair specific for 24 different genetic markers. Moreover, the primers are defined in terms of the result to be achieved, namely by their specificity for the said 24 different genetic markers (supra) (Art. 6 PCT).

Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely a kit as defined by claim 52, wherein the primer pairs specific for RD4 and RD5 are those given in Table 3.

The nucleic acid referred to in claim 57 is defined by reference to claim 53 which, however, does not relate to any nucleic acids. Claim 57 was thus interpreted as referring to claim 56 (Art. 6 PCT).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Internal Publication No
PCT/IB 0986

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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